PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25667A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003396	International filing date *(day/month/year)* 18.10.2004	Priority date *(day/month/year)* 31.10.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K31/505 A61K38/46 A01K67/027 C12N5/06 C12N15/11		
Applicant PFIZER PRODUCTS INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand 26.11.2004	Date of completion of this report 05.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Durrenberger, A Telephone No. +49 89 2399-

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-43 as originally filed

   Sequence listings part of the description, Pages

   1-2 as originally filed

   Claims, Numbers

   1-15 as originally filed

   Drawings, Sheets

   1/10-10/10 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6, 13, 15

because:

☒ the said international application, or the said claims Nos. 1-6 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-6, 15 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-6, 15 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 13

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-14
	No:	Claims	1-6,15
Inventive step (IS)	Yes:	Claims	7-14
	No:	Claims	1-6,15
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see separate sheet

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Concerning section III

1. Claims 1-6 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Present claims 1-6 and 15 relate to compounds defined by reference to a desirable characteristic or property, namely their ability to inhibit PDE9 (see in particular p. 4, l. 29 to p. 5, l. 19).
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved.
Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the description at page 13, line 1 to p. 14, line 30 and the antisenses of SEQ. ID. NO. 1 and 2.

3. The subject-matter of claim 13 covers human embryonic stem cells. The applicant's attention is drawn on the fact that the use of human embryonic cells for industrial or commercial purposes, as encompassed in the claims, may not be allowable in certain Contracting States.

Concerning section V

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 03/037432 A (PFIZER PRODUCTS INC; FRYBURG, DAVID, ALBERT; GIBBS, EARL, MICHAEL) 8 May 2003 (2003-05-08)
D2: WO 03/061638 A (LAUTT, WAYNE, W; MACEDO, PAULA; DIAMEDICA INC) 31 July 2003 (2003-07-31)
D3: US 2003/166662 A1 (FRYBURG DAVID ALBERT ET AL) 4 September 2003 (2003-09-04)
D4: US-B1-6 255 456 (FISHER DOUGLAS A ET AL) 3 July 2001 (2001-07-03)
D5: WO 00/47206 A (NOVO NORDISK A/S) 17 August 2000 (2000-08-17)
D6: WO 03/028730 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; COHEN) 10 April 2003 (2003-04-10)
D7: DOUSA T P: "Cyclic-3',5'-nucleotide phosphodiesterase isozymes in cell biology and pathophysiology of the kidney" KIDNEY INTERNATIONAL, NEW YORK, NY, US, vol. 55, no. 1, 1999, pages 29-62, XP002169142 ISSN: 0085-2538
D8: FISHER D A ET AL: "Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 273, no. 25, 19 June 1998 (1998-06-19), pages 15559-15564, XP002091363 ISSN: 0021-9258
D9: SODERLING S H ET AL: "Identification and characterization of a novel family of cyclic nucleotide phosphoiesterase" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 273, no. 25, 19 June 1998 (1998-06-19), pages 15553-15558, XP002127167 ISSN: 0021-9258
D10: US 2004/220186 A1 (BELL ANDREW SIMON ET AL) 4 November 2004 (2004-11-04)

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6 is not new in the sense of Article 33(2) PCT:
- the document D1 discloses the inhibitors of the present invention as cited on page 13, line 3, in the treatment of obesity in individuals having insulin resistance syndrome.

- D2 discloses the use of zaprinast, which is a non-selective inhibitor of PDE9 (see D7 and D8), in the treatment of obesity in individuals having insulin resistance syndrome.
- D3 discloses the use of Sch-51866, which is a non-selective inhibitor of PDE9 (see D7 and D9), in the treatment of obesity in individuals having insulin resistance syndrome.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT in view of D4 which discloses antisenses to PDE9A.

3. The claimed invention is based on the discovery that
i) PDE9 knock-out (claims 7-14) mice show decreased body weight and
ii) the administration to *ob/ob* mice of one pyrimidine derivative (Compound A disclosed on page 13, lines 8-9), results in decreased glucose, triglycerides and fructosamine (claims 1-6, 15).

i) The subject-matter of claims 7-14 is novel and inventive because this teaching could not be derived from the prior art.

ii) In case novelty of claims 1-6 is established, its subject-matter would not be inventive: the documents D1 to D3, D5, D6 disclose the use of pyrimidine derivatives in the treatment of obesity. Hence the selection of derivatives not yet disclosed in the treatment of obesity does not need any particular inventive skills for the skilled person in the absence of an unexpected technical effect over the compounds of the art. In particular, the application discloses only the effect of one precise derivative, i.e. "compound A", which does not have a surprising technical effect over the structurally similar derivatives disclosed in the art.
Concerning compounds for which no technical data are present, no inventive activity can be recognized as they do not solve the problem of providing alternative compounds for treating obesity.

4. For the assessment of the present claims 1-6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Concerning section VIII

The application does not meet the requirements for clarity of Art. 6 PCT for the following reasons:

- the broad wording "PDE9 inhibitor" in claims 1-6 includes compounds for which no structure is given (e.g. antisenses, amino acids, small molecules, etc, cf. p. 4, lines 25 to 34);

- the same objection applies to the functional definition of claim 15. Protection for SEQ ID NOS: 1 and 2 only can be claimed.